UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/759,360	01/16/2001	Wolfgang Halfbrodt	SCH-1738	1922

7590 07/11/2005

MILLEN, WHITE, ZELANO & BRANIGAN. P.C.
Arlingotn Courthouse Plaza I
Suite 1400
2200 Clarendon Boulevard
Arlington, VA 22201

EXAMINER	
ROBINSON, BINTA M	

ART UNIT	PAPER NUMBER
1625	

DATE MAILED: 07/11/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/759,360	HALFBRODT ET AL.	
	Examiner	Art Unit	
	Binta M. Robinson	1625	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *15-24,26,29,30,32-38,40 and 42-44* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *15-24,26,29,30,32-38,40 and 42-44* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *6/30/04*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

Detailed Action

The 112 first paragraph rejection of claims 15-24, 26, 29, 30, 32, 33, 34, 35, 36, 37, 38, 40, 42 is maintained in the office action mailed 10/6/04. The 112, first paragraph rejection is added for claims 43-44. The restriction requirement at office action filed 3/23/04 has been reinstated because of the burden of search to examine the myriad of independent and distinct inventions. Group I as defined in the office action mailed 3/23/04 has been examined. The restriction is FINAL.

(new objections)

The numbering of claims is not in accordance with 37 CFR 1.126 which requires the original numbering of the claims to be preserved throughout the prosecution. When claims are canceled, the remaining claims must not be renumbered. When new claims are presented, they must be numbered consecutively beginning with the number next following the highest numbered claims previously presented (whether entered or not).

Misnumbered claim 43 has been renumbered 44.

Applicant is advised that should claim 35 be found allowable, claim 36 will be objected to under 37 CFR 1.75 as being a substantial duplicate thereof. When two claims in an application are duplicates or else are so close in content that they both cover the same thing, despite a slight difference in wording, it is proper after allowing one claim to object to the other as being a substantial duplicate of the allowed claim. See MPEP § 706.03(k).

Claim 42 is objected to because the words "pyrrolidin", "morpholin", and "piperidin" are misspelled. The terms should be spelled correctly as "pyrrolidine, morpholine, piperidine".

(Modified rejection)

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 15-24, 26, 29, 30, 32, 33, 34, 35, 36, 37, 38, 40, 42, 43, 44 are rejected under 35 U.S.C. 112, first paragraph, because the specification, does not reasonably provide enablement for a method of treating a patient suffering from chronic inflammation or a disease associated with chronic inflammation with the instant compounds, and particularly does not provide enablement for the treatment of all tumors in claim 43. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

There are many factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is "undue". These factors include 1)the breadth of the claims, 2) the nature of the invention, 3) the state of the prior art, 4) the level of one of ordinary skill, 5) the level of predictability in the art 6) the amount of direction provided by the inventor

7) the existence of working examples, and 8) the quantity of experimentation needed to make or use the invention based on the content of the disclosure. In re Wands, 858 F. 2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988).

In terms of factor 3 and 5, the state of the art and the level of predictability in the art cannot be predicted with any certainty beyond what specific test compounds /compositions and/or additional therapeutic agents should be used and are likely to provide productive results beyond those therapeutic compounds/compositions and/or additional therapeutic agents taught in the specification. There is no indication, which compounds where tested for their effect on microglial activation.

The nature of the invention

The nature of the invention is the synthesis of novel benzimidazole compounds and their use in the treatment and prophylaxis of chronic inflammation and diseases associated with microglia activation.

The state of the prior art

The state of the prior art is that a central step of the inflammation process is the activation of microglia. This is carried out in diseases such as Alzheimer's disease. The microglia can remain for a prolonged period in the activated state, in which they produce and secrete various inflammation factors. These factors produce neuronal dysfunction and degeneration. Treatment of neuroinflammation to date has been with steroidal anti-inflammatory agents see page 1 of the specification, cytokine modulators, page 2 of the specification, and complement-cascade-inhibitors, see page 2 of the specification. These substances inhibit the syntheses or the action of

individual inflammation factors. However, the claimed invention sets out to inhibit an earlier step in the inflammation process and thus prevent the development of any inflammatory factors. Minocycline has been shown to block microglial activation of 6-hydroxydopamine and 1-methyl-4-phenyl-1,2,3-6-tetrahydropyridine-lesioned parkinsonism animal models. See abstract on page 679 of Thomas et. al. However, no clinical trials published to the date of the publication of the Thomas et. al., article have been conducted on the use of MC for the management of Parkinson's disease. See page 684, of Thomas et. al. However, inhibitors of microglial activation have not been known in the art to treat chronic inflammation itself or diseases or Parkinson's disease that are associated with chronic inflammation.

The predictability or lack thereof in the art

The instant claimed invention is highly unpredictable as discussed below:

In the instant case, the claimed invention is highly unpredictable because of the absence of the claiming of the actual diseases that are said to be associated with microglial activation. The applicant has not shown that by inhibiting microglial activation, that specific diseases are being treated. The nature of this art is that it involves screening in vitro and in vivo

to determine which compounds exhibit the desired pharmacological activities. There is no absolute predictability even in view of the seemingly high level of skill in the art. The existence of these obstacles establishes that the contemporary knowledge in the art would prevent one of ordinary skill in the art from accepting any therapeutic regimen on its face. Regarding claim 43, Cancer treatment is highly

specific and unpredictable. While specific compounds can treat particular tumors, it is unpredictable to extrapolate in generality to all tumors. Tumor classification can be by type of tissue in which the cancer originates or by primary site.

The amount of direction or guidance present

The direction present in the instant specification is that the instant compounds can inhibit microglial activation which helps in the treatment of diseases such as Alzheimer's which is said to be mediated by microglial activation. However, the specification fails to provide a correlation between the diseases listed in the specification and the inhibition of microglial activation. The specification fails to provide any experimental data of the effect of these compounds on microglial activation and specific diseases correlated with microglial activation.

The presence or absence of working examples

The applicant provides no working examples for the treatment of diseases association with microglial activation. Also, the compounds, which are disclosed in the specification, have no pharmacological data regarding the treatment of any disease. Also, the specification fails to provide working examples as to how the diseases associated with microglial activation in the specification can be treated by inhibition of microglial activation.

The breadth of the claims

The breadth of the claims of this 112 rejection, is that the compounds can treat chronic inflammation, diseases associated with microglial activation as well as the specific diseases claimed in claim 33, 37, 43.

The quantify of experimentation needed

The quantity of experimentation needed is undue experimentation. One of skill in the art would need to determine what specific diseases would be benefited by the inhibition of microglial activation and would furthermore then have to determine whether the claimed compounds would provide treatment of the disease by the inhibition of microglial activation.

The level of skill in the art

The level of skill in the art is high. However, due to the unpredictability in the art, it is noted that each embodiment of the invention is required to be individually assessed for physiological activity by in vitro and in vivo screening to determine which compounds exhibit the desired pharmacological activity and which diseases would benefit this activity.

Thus, the specification fails to provide sufficient support of the broad use of the compound for the treatment of all chronic inflammation and all diseases associated with microglial activation. As a result, necessitating one of skill to perform an exhaustive search for which chronic inflammation can be treated by the claimed compound in order to practice the claimed invention.

Genentech Inc. v. Novo Nordisk A/S (CA FC) 42 USPQ2d 1001 , states that " a patent is not a hunting license. It is not a reward for search , but compensation for its successful conclusion" and "[p]atent protection is granted in return for an enabling

disclosure of an invention, not for vague intimations of general ideas that may or may not be workable".

Therefore, in view of the Wands factors and In re Fisher (CCPA 1970) discussed above, to practice the claimed invention herein, a person of skill in the art would have to engage in undue experimentation to test which microglial activation associated diseases can be treated by the compound encompassed in the instant claims, with no assurance of success.

Working examples

There is no indication, which compounds where tested for their effect on microglial activation. An indeterminate quantity of experimentation would be necessary to determine all potential therapeutic compounds/compositions' effects on microglia activation.

Quantity of experimentation

In terms of the 8th Wands factors, undue experimentation would be required to make or use the invention based on the content of the disclosure due to the breadth of the claims, the level of predictability in the art of the invention, and the poor amount of direction provided by the inventor. Taking the above factors into consideration, it is not seen where the instant claim is enabled by the instant application.

(new rejections)

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter, which the applicant regards as his invention.

Claim 43 recites the limitation of the specific diseases in 2-6 in claim 43 and line 2 of claim 43. There is insufficient antecedent basis for this limitation in the claim. Many of these diseases are associated with inflammation, but they are not all equivalent to chronic inflammation. For example there are several risk factors in addition to inflammation that may play a role in Alzheimer's disease and Down syndrome. See 2005:20310 Hcaplus. Additionally, the etiology of multiple sclerosis is unknown, although both genetic and environmental contributions do contribute to its pathogenesis. See Hcaplus 132:206042.

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claim(s) 43 is rejected under 35 U.S.C. 102(b) as being anticipated by Lunn et. al. (See Reference W). Lunn discloses the instant method of treating conditions associated with B-amyloid peptide such as Alzheimer's disease or Down's syndrome with compound, RN 175714-04-2. At Hcaplus 125:300996, see the instant method.

Claims 15, 16, 17, 18, 19, 20, 21, 22,23, 24, 29, 30, 32, 33, 34, 37, 38, 40 42, 43, 44 are rejected under 35 U. S. C. 102 (b) as being anticipated by Burns et. al. (See Reference X). Burns discloses the instant method of treating inflammatory diseases with the compound, RN 175714-04-2. At Hcaplus 124:289536, see the instant method.

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 43 is rejected under 35 U.S.C. 103(a) as being unpatentable over Lunn et. al (See Reference A) in view of Hcaplus 122:236400 (See Reference U1).Lunn et. al. teaches the instant method of treating a condition associated with Beta-amyloid peptide-associated neurotoxicity with a compound as depicted at column 57, lines 20-30, wherein R^1 is phenyl, which is optionally substituted with halo, C_1-C_6 alkoxy, nitro, amino, cyano, C_1-C_6 alkylamino and C_1-C_6 alkylthio, R^2 is napthyl which may be optionally substituted with hydroxyl, halo, C_1-C_6 alkoxy, nitro, amino, cyano, C_1-C_6 alkylamino, R^3 is C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 alkylthio or is R_4R_5N-(C_1-C_6alkylidenyl)- wherein R4 and R5 can be C_1-C_6 alkyl or hydrogen and that benzididazoles are known for their anti-inflammatory activities (See column 6, lines 20-24). At column 57, see the instant method of treating a condition associated with Beta-amyloid peptide-associated neurotoxicity with a compound as depicted at column 57, lines 20-30. The difference between the prior art method and the instantly claimed method is the teaching of a method of treating conditions associated with Beta-amyloid pepitide associated neurotoxicity such as Down's syndrome or Alzheimer's Disease with a genus of compounds versus a method of treating these diseases with a subgenus of compounds as disclosed in the prior art. Hcaplus 122:236400 teaches that chronic inflammation is a part of pathological process of some of the diseases listed in claim 43,

such as Alzheimer's disease. It would have been obvious to one of ordinary skill in the art to select various known radicals within a genus to prepare structurally similar compounds and to use these compounds to treat the claimed diseases. For instance, see the compound, the method of treating these diseases with RN 175714-04-2 At Hcaplus 125:300996. Accordingly, the method is deemed unpatentable therefrom in the absence of a showing of unexpected results for the claimed method over those of the prior art method.

Claims 15, 16, 17, 18, 19, 20, 21, 22,23, 24, 29, 30, 32, 33, 34, 37, 38, 40 42, 43, 44 are rejected under 35 U.S.C. 103(a) as being unpatentable over Bruns et. al. (See Reference N).

Brus et. al. teaches the instant method of treating a condition associated with Beta-amyloid peptide-associated neurotoxicity with a compound as depicted at column 57, lines 20-30, wherein R^1 is phenyl, which is optionally substituted with halo, C_1-C_6 alkoxy, nitro, amino, cyano, C_1-C_6 alkylamino and C_1-C_6 alkylthio, R^2 is napthyl which may be optionally substituted with hydroxyl, halo, C_1-C_6 alkoxy, nitro, amino, cyano, C_1-C_6 alkylamino, R^3 is C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 alkylthio or is R_4R_5N-(C_1-C_6alkylidenyl)- wherein R4 and R5 can be C_1-C_6 alkyl or hydrogen. At page 69, lines 15-50, see the compound depicted and at page 63, lines 17-20, see the method of using the compounds of formula I to treat inflammatory diseases and disorders such as Alzheimer's disease and Down's syndrome. The difference between the prior art method and the instantly claimed method is the teaching of a method of treating with a genus versus subgenus of compounds as disclosed in the prior art. It would have been

obvious to one of ordinary skill in the art to select various known radicals within a genus to prepare structurally similar compounds and to use these compounds to treat the claimed diseases. For instance, see the compound, the method of treating these diseases with RN 175714-04-2 at Ca 124:289536. Accordingly, the method is deemed unpatentable therefrom in the absence of a showing of unexpected results for the claimed method over those of the prior art method.

Response to Applicant's Remarks

The applicant asserts that the examiner improperly bases the 112, first paragraph rejection on the lack of clinical trials and FDA standards. However, the examiner has not based the 112, first paragraph rejection on FDA standards, but has considered several of the Wands factors cumulatively. At the time the invention was filed, inhibitors of microglial activation had not been known in the art to treat chronic inflammation itself or diseases or Parkinson's disease that are associated with chronic inflammation. There are various types of chronic inflammation, which manifests itself in various disease conditions. However, in the absence of a showing in the prior art at the time the invention was filed, that inhibitors of microglial activation can treat chronic inflammation and diseases associated with it, the applicant has not sufficiently shown sufficient data in the specification that the claimed compounds can treat chronic inflammation with great efficacy. There is no indication, which compounds where tested for their effect on microglial activation. An indeterminate quantity of experimentation would be necessary to determine all potential therapeutic compounds/compositions' effects on microglia activation.

The IDS filed 6/30/04 has been considered.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Binta M. Robinson whose telephone number is (571) 272-0692. The examiner can normally be reached on M-F (9:30-6:00).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Cecilia Tsang can be reached on 571-272-0562.

A facsimile center has been established. The hours of operation are Monday through Friday, 8:45 AM to 4:45 PM. The telecopier numbers for accessing the facsimile machine are (703)308-4242, (703)305-3592, and (703)305-3014.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (571)-272-1600.

BMR
July 1, 2005

Cecilia J. Tsang
Supervisory Patent Examiner
Technology Center 1600